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Alterations in Left Ventricular Diastolic Function With Doxorubicin Therapy

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To determine whether impaired diastolic function may be an early sign of doxorubicin cardiotoxicity, a retrospective study was performed in 12 patients who had undergone serial radionuclide angiography and were found to have a left ventricular ejection fraction of 55% or more before doxorubicin (Adriamycin) treatment and during follow-up. Average rapid filling velocity and slow filling velocity were both significantly reduced after doxorubicin treatment. Rapid filling velocity decreased from 5.17 ± 1.52 to 4.18 ± 0.96 units/s ($p < 0.01$), and slow filling velocity decreased from 2.20 ± 1.32 to 1.42 ± 0.62 units/s ($p < 0.05$). There were no significant changes in filling volume ratio, total diastolic time or diastolic time ratio.

Because a change in left ventricular diastolic function can occur before ejection fraction falls to subnormal levels, diastolic function as well as systolic function should be examined for the early detection of doxorubicin cardiotoxicity. The clinical implications of our observations can only be established by a longer-term prospective analysis of left ventricular function in patients receiving doxorubicin therapy.

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Doxorubicin (Adriamycin) is an anthracycline antibiotic agent that is effective in the treatment of various solid tumors and hematologic malignancies (1,2). Owing to its dose-related cardiac toxicity (3,4), the usefulness of this drug is limited to treatment durations of usually less than 1 year, and responders may require discontinuation of effective treatment. Although clinical congestive heart failure occurs in up to one-third of patients receiving a total dose of more than 550 mg/m^2 body surface area (3,4), patients may develop heart failure at a lower total dose (1,5–7). Consequently, clinically sensitive tests are needed to select patients in whom treatment must be stopped early.

Various techniques have been used for early detection of subclinical doxorubicin-induced cardiomyopathy, including electrocardiography (8,9), systolic time intervals (10,11), echocardiography (12–14), radionuclide angiography (6,7,15–17) and endomyocardial biopsy (17–19). Most studies of doxorubicin cardiotoxicity have dealt with systolic function of the left ventricle, and effects on diastolic function have not been reported. The purpose of this study was to evaluate whether doxorubicin can alter left ventricular diastolic function before changes in systolic function are evident.

Methods

Patient selection. Because of the retrospective nature of this study, this protocol was designated as exempted research by the Human Research Committee. Records were reviewed of all patients who had radionuclide angiography both before and after doxorubicin therapy between January 1982 and February 1985 at the Medical College of Ohio Hospital. Those patients were selected for study who had left ventricular ejection fractions of 55% or more by radionuclide angiography both before the first dose of doxorubicin and during the follow-up period; there were 12 such patients.

All patients except one were female. Ages ranged from 16 to 69 years (mean 53.3). Five patients had ovarian cancer and of the remaining seven patients, one each had endometrial cancer, cervical cancer, carcinoid tumor, Hodgkin's lymphoma, Ewing's sarcoma, breast cancer and leiomyo-

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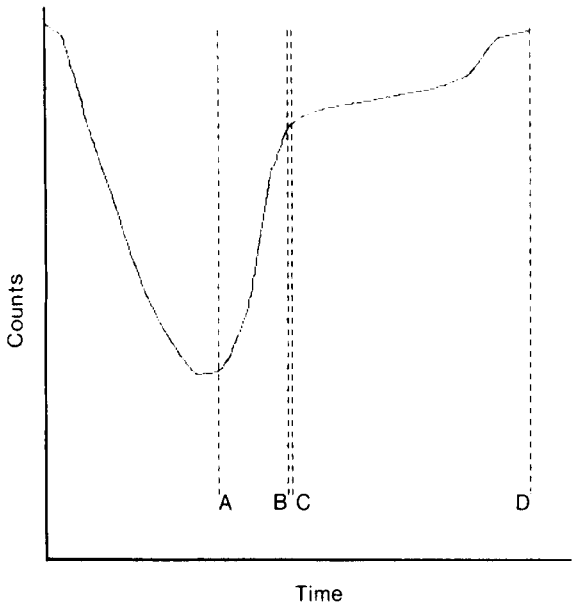

Figure 1. Left ventricular time-activity curve. A = start of rapid filling; B = end of rapid filling; C = start of slow filling; D = end of slow filling. Rapid filling time = A to B, slow filling time = C to D and total diastolic time = A to D.

sarcoma. No patient had a history of mediastinal irradiation. Two had hypertension.

Drug administration. Patients received doxorubicin in doses ranging from 80 to 448 mg/m^2 body surface area (mean 193 ± 102). Most patients received the drug as a single bolus intravenous injection every 3 to 4 weeks. One patient received doxorubicin for 4 consecutive days every 4 weeks. All patients except one were given doxorubicin in combination with cyclophosphamide, cis-platin, vinblastine or thio-TEPA. No patient developed clinical evidence of heart failure.

Protocol. Two multigated radionuclide angiograms were reviewed for each patient. The first was obtained before doxorubicin therapy was initiated; the second was obtained after the course of doxorubicin therapy was completed. The mean interval from the first dose of doxorubicin to the second radionuclide angiogram was 110 days (range 72 to 241) and from the last dose of doxorubicin to the second study was 27 days (range 7 to 43).

Radionuclide angiography. The study was performed with patients in the supine position using red blood cells tagged with 20 mCi of technetium-99m pyrophosphate (20). Counts were acquired in the left anterior oblique view showing best separation of right and left ventricles, using a Technicare Sigma 120 portable gamma camera, equipped with a GAP collimator and interfaced to a Technicare MCS 560 portable computer. Electrocardiographic-gated images were used to collect data into 16 frames, each frame having a duration of 1/16th of the RR interval, and an average left ventricular count value of 125 counts/pixel. Data were stored on floppy disks in a 64 × 64 matrix with a pixel size of 2.4 mm. After completion of imaging, time-activity curves and left ventricular ejection fraction were computed using Technicare software. The ejection fraction was calculated by subtracting the left ventricular end-systolic counts from end-diastolic counts, and dividing the result by left ventricular end-diastolic counts.

Diastolic function variables. Diastolic function curves were examined in a manner similar to that of Smith et al. (21). Several measurements were calculated from the time-activity curve (Fig. 1). Four diastolic points were marked by the operator, indicating 1) start of rapid filling, 2) end of rapid filling, 3) start of slow filling, and 4) end of slow filling. From counts and time at these points, the following variables were calculated:

Rapid filling velocity and slow filling velocity. A regression line was plotted for counts versus time between start

Table 1. Variables Before and After Doxorubicin Therapy in 12 Patients

	Pre-DXR	Post-DXR	p Value
Heart rate (beats/min)	88 ± 15	82 ± 12	NS
Blood pressure (mm Hg)			
Systolic	124 ± 21	122 ± 18	NS
Diastolic	76 ± 9	78 ± 10	NS
Systolic function			
EF (%)	64 ± 6	61 ± 7	NS
Diastolic function			
RFV (units/s)	5.17 ± 1.52	4.18 ± 0.96	<0.01
SFV (units/s)	2.20 ± 1.32	1.42 ± 0.62	<0.05
FVR	0.61 ± 0.16	0.71 ± 0.14	NS
RFT (ms)	121.78 ± 37.51	148.97 ± 50.95	NS
TDT (ms)	255.87 ± 81.63	271.02 ± 17.73	NS
DTR	0.50 ± 0.13	0.55 ± 0.15	NS

Values are ± SD. DTR = diastolic time ratio; DXR = doxorubicin; EF = ejection fraction; FVR = filling volume ratio; RFT = rapid filling time; RFV = rapid filling velocity; SFV = slow filling velocity; TDT = total diastolic time.

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and end of rapid filling and between start and end of slow filling. Average rapid and slow filling velocities were taken as the slopes of these regression lines in counts per second divided by the end-diastolic counts and expressed as units/second.

Filling volume ratio. The ratio of rapid filling volume to rapid plus slow filling volume was defined as: filling volume ratio = (counts at ERF − SRF)/(counts at ESF − SRF), ERF and SRF = end and start, respectively, of rapid filling.

Rapid filling time, total diastolic time and diastolic time ratio. The duration of rapid and slow filling times and the ratio of rapid filling time to total diastolic time (diastolic time ratio) were also calculated from the points marked on the time-activity curve.

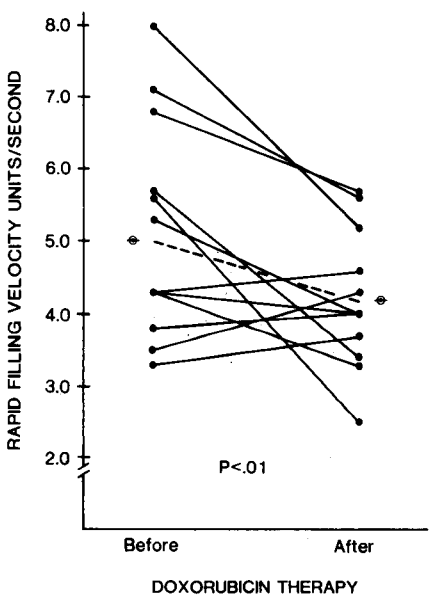
Statistics. Statistical comparisons were made by the paired *t* test. Correlations were performed using Pearson's correlation coefficient.

Results

Ejection fraction. Heart rate and blood pressure were not significantly changed from pretreatment values after doxorubicin therapy. There was no significant decrease in left ventricular ejection fraction after doxorubicin, ejection fraction remaining greater than 55% before and after doxorubicin therapy as expected by selection criteria for these 12 patients (Table 1).

Average rapid left ventricular filling velocity showed a significant decrease after doxorubicin therapy ($p < 0.01$) (Table 1, Fig. 2). No significant correlation was found between the change in average rapid filling velocity and the change in ejection fraction ($r = 0.43$, $p > 0.05$). There was also a significant reduction in average slow filling velocity ($p < 0.05$) (Table 1, Fig. 3). Rapid filling time was insignificantly prolonged. There were no significant changes in diastolic filling volume ratio, total diastolic time and diastolic time ratio after doxorubicin. No correlation was found between the cumulative doxorubicin dose and changes in diastolic variables.

Figure 2. Rapid filling velocity before and after doxorubicin therapy in 12 patients.



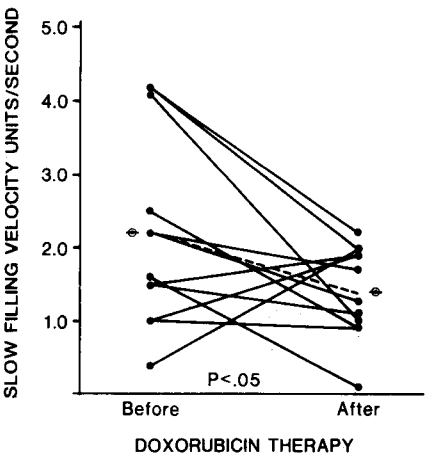


Figure 3. Slow filling velocity before and after doxorubicin therapy in 12 patients.

Discussion

The clinical syndrome of doxorubicin-induced cardiomyopathy is related to the total dose administered (3,4). Because of this dose-related cardiotoxicity, early inappropriate discontinuation of doxorubicin therapy may minimize its therapeutic efficacy in many patients. Previous attempts designed to predict the presence of subclinical doxorubicin cardiomyopathy by noninvasive assessment of left ventricular systolic function have been reported (6–18) but have not resulted in establishment of a sensitive means of early detection.

Diastolic dysfunction. Myocardial contraction and relaxation are loosely coupled processes that may be separately influenced by certain stimuli (22). Diastolic impairment may therefore occur in the absence of systolic dysfunction and may develop coincident with or even before abnormalities of systolic performance (23,24). Reports of the occurrence of diastolic dysfunction with little or no systolic impairment in various heart diseases such as coronary artery disease (25–27), volume overload and pressure overload states (28–30) and cardiomyopathy (31) led us to investigate this phenomenon in patients who received doxorubicin and who maintained a normal ejection fraction. The present study suggests that gated radionuclide angiography can be used to detect doxorubicin-induced diastolic dysfunction before there is evidence of systolic dysfunction or clinical evidence of cardiotoxicity.

Of the six variables of diastolic function tested, only two showed significant changes: rapid and slow filling velocity. The change in average rapid filling velocity was more significant than the change in slow filling velocity. We employed average filling velocities as measures of diastolic function. Although previous studies (25,26,29) have used the peak rate of filling as an indication of diastolic function, that measurement is extremely dependent on fine temporal resolution. Although average filling velocities are less sensitive to noise, they are not independent of temporal resolution. We attempted to minimize heart rate variability by setting a gate for each patient to reject beats with a cycle length that was greater than 20% different from the average for that patient.

Our methods for measuring average filling velocities differ slightly from those reported by Smith et al. (21) in that only the relatively constant portions of the rapid and slow filling phases were used in our study. Thus by not taking the minimal count point of the curve as the onset of rapid filling, we attempted to avoid an error in slope calculation that might occur if a variable portion of the isovolumic region of the time-activity curve was included. As a result, our method yielded more rapid normal velocities than the average rates reported by Smith et al. (21).

Cardiotoxicity at low dosage. The cumulative doses of doxorubicin given our patients were relatively low (mean 193 mg/m^2). Although congestive heart failure develops more frequently after doxorubicin therapy at cumulative doses in excess of 550 mg/m^2, it has been reported to occur in 3.5% of patients given 400 mg/m^2 (32) and even in some patients given less than 200 mg/m^2 (11,32). In our study the lowest total dose of doxorubicin received by a patient who developed diastolic dysfunction was 166 mg/m^2.

Bristow et al. (18) initially reported on nine patients treated with doxorubicin without mediastinal radiation who had mild histopathologic changes in endomyocardial biopsy specimens when the cumulative dose was less than 300 mg/m^2 and on two patients when the dose was less than 200 mg/m^2. The extent of morphologic change on biopsy was proportional to the total dose administered throughout a dose range of 45 to 545 mg/m^2. Cardiac function changes measured from systolic time intervals were not encountered at doses less than 400 mg/m^2. Bristow et al. (33) later expanded these observations in a study in which left ventricular function was assessed by echocardiographically derived percent fractional shortening. There was little change in cardiac function at total doses less than 300 mg/m^2 although biopsy changes were encountered at doses of 100 to 300 mg/m^2.

Mechanism of diastolic dysfunction. The mechanism for abnormal left ventricular diastolic filling induced by doxorubicin is unknown. It may be that reduction in left ventricular adenosine triphosphate levels caused by impaired mitochondrial oxidative function in patients receiving doxorubicin (34,35) could inhibit calcium uptake by the sarcoplasmic reticulum and might account for the abnormalities in diastolic filling. The determinants of diastolic function are multifactorial, and we do not know which factors may have changed with doxorubicin therapy. Because these studies were noninvasive, ventricular pressure-volume relations were not examined. Several investigators (36,37) have pointed out that increases in heart rate and blood pressure may cause changes in measures of diastolic left ventricular function, but there were no significant changes in heart rate and blood pressure in our patients.

Risk factors for cardiotoxicity. An increased risk of clinically apparent cardiotoxicity has been reported in patients receiving less than 500 mg/m^2 of doxorubicin, if other cardiotoxic factors, such as combination anticancer therapy (8,9,32,38), previous mediastinal irradiation (5,8,9), hypertension (8) or other heart disease (5) are present.

Age over 70 years has also been cited as an independent risk factor for development of doxorubicin-associated heart failure (18). None of our patients were 70 years of age or older. Although 2 of our 12 patients were hypertensive, we found no relation between their blood pressures and the extent of change in diastolic function. None of our patients had pericardial effusion and none had received radiation therapy that might impair diastolic performance. Whether the concomitant administration of cyclophosphamide, vinblastine and thio-TEPA with doxorubicin in the present study had any influence on the diastolic impairment we observed cannot be evaluated from our data. Thus, the altered diastolic filling velocities encountered in our patients after doxorubicin administration are not explained by age, by concurrent hemodynamic changes or by the effects of other therapeutic interventions.

Conclusions. In a highly selected group of patients who received doxorubicin in doses of less than 200 mg/m^2, we found evidence of impaired left ventricular diastolic function without significant reduction in systolic function. Radionuclide assessment of diastolic as well as systolic function may be of value in the evaluation of the progressive deterioration of cardiac function associated with doxorubicin therapy. A prospective study involving serial measurements at different doses will be required to evaluate the role of diastolic dysfunction in the early detection of cardiotoxicity.

References

1. Blum RH, Carter SK. Adriamycin: a new anticancer drug with significant clinical activity. Ann Intern Med 1974;80:249–59.
2. Benjamin RS, Wiernik PH, Bachur NR. Adriamycin chemotherapy: efficacy, safety, and pharmacologic basis of an intermittent single high-dosage schedule. Cancer 1974;33:19–27.
3. Lefrak EA, Pitha J, Rosenheim S, Gottlieb JA. A clinicopathologic analysis of Adriamycin cardiotoxicity. Cancer 1977;39:1397–402.
4. Minow RA, Benjamin RS, Lee ET, Gottlieb JA. Adriamycin cardiomyopathy: risk factors. Cancer 1977;39:1397–402.
5. Cortes EP, Lutman G, Wanka J, et al. Adriamycin (NSC 123127)

cardiotoxicity: a clinicopathologic correlation. Cancer Chemother Rep 1975;6(part 3):215–25.

6. Alexander J, Dainiak N, Berger HJ, et al. Serial assessment of doxorubicin cardiotoxicity with quantitative radionuclide angiocardiography. N Engl J Med 1979;300:278–83.
7. Gottdiener JS, Mathisen DJ, Borer JS, et al. Doxorubicin cardiotoxicity: assessment of late left ventricular dysfunction by radionuclide cineangiography. Ann Intern Med 1981;94:430–45.
8. Minow RA, Benjamin RS, Gottlieb JA. Adriamycin (NSC-123127) cardiomyopathy: an overview with determination of risk factors. Cancer Chemother Rep 1975;6(part 3):195–201.
9. Minow RA, Benjamin RS, Lee ET, Gottlieb JA. QRS voltage change with Adriamycin administration. Cancer Treat Rep 1978;62:931–4.
10. Rinehart JJ, Lew RP, Balcerzak SP. Adriamycin cardiotoxicity in man. Ann Intern Med 1974;81:475–8.
11. Balcerzak SP, Christakis J, Lewis RP, Olson HM, Malspeis L. Systolic time intervals in monitoring Adriamycin-induced cardiotoxicity. Cancer Treat Rep 1978;62:893–9.
12. Bloom KR, Bini RM, Williams CM, Sonley MJ, Gribbin MA. Echocardiography in Adriamycin cardiotoxicity. Cancer 1978;41:1265–9.
13. Henderson IC, Sloss LJ, Laffe N, et al. Serial studies of cardiac function in patients receiving Adriamycin. Cancer Treat Rep 1978;62:923–9.
14. Borow KM, Henderson IC, Neuman A, et al. Assessment of left ventricular contractility in patients receiving doxorubicin. Ann Intern Med 1983;99:750–6.
15. Singer JW, Narahara KA, Ritchie JL, Hamilton GW, Kennedy JW. Time- and dose-dependent changes in ejection fraction determined by radionuclide angiography after anthracycline therapy. Cancer Treat Rep 1978;62:945–8.
16. Green MD, Speyer JL, Muggia FM. Anthracycline cardiotoxicity: a perspective from current clinical studies. Cancer Treat Rep 1983;1:71–3.
17. Druck MN, Gulenchyn KY, Evans WK, et al. Radionuclide angiography and endomyocardial biopsy in the assessment of doxorubicin cardiotoxicity. Cancer 1984;53:1667–74.
18. Bristow ME, Mason JW, Billingham ME, Daniels JR. Doxorubicin cardiomyopathy: evaluation by phonocardiography, endomyocardial biopsy, and cardiac catheterization. Ann Intern Med 1978;88:168–75.
19. Ewer MS, Ali K, Mackay B, et al. A comparison of cardiac biopsy grades and ejection fraction estimations in patients receiving Adriamycin. J Clin Oncol 1984;2:112–7.
20. Thrall JH, Freitas JE, Swanson D, et al. Clinical comparison of cardiac blood pool visualization with technetium-99m red blood cells labelled in vivo and with technetium-99m human serum albumin. J Nucl Med 1978;19:796–803.
21. Smith VE, Schulman P, Karimeddini M, et al. Rapid ventricular filling in left ventricular hypertrophy. II. Pathologic hypertrophy. J Am Coll Cardiol 1985;5:869–74.
22. Parmley WW, Sonnenblick EH. Relation between mechanics of contraction and relaxation in mammalian cardiac muscle. Am J Physiol 1969;216:1084–91.
23. Mann T, Goldberg S, Mudge GH, Grossman W. Factors contributing to altered left ventricular diastolic properties during angina pectoris. Circulation 1979;59:14–20.
24. Grossman W, McLaurin LP. Diastolic properties of the left ventricle. Ann Intern Med 1976;84:316–26.
25. Gaasch WH, Levine HJ, Quinones MA. Left ventricular compliance: mechanisms and clinical implications. Am J Cardiol 1976;38:645–53.
26. Bonow RO, Bacharach SL, Green MV, et al. Impaired left ventricular diastolic filling in patients with coronary artery diseases. Assessment with radionuclide angiography. Circulation 1981;64:315–23.
27. Reduto LA, Wickemeyer WJ, Young JB, et al. Left ventricular diastolic performance at rest and during exercise in patients with coronary artery disease. Circulation 1981;63:1228–37.
28. Qureshi S, Wagner HN, Anderson PP. Evaluation of left ventricular function in normal persons and patients with heart disease. J Nucl Med 1978;19:135–41.
29. Fouad FM, Tarazi RC, Gallagher JH, et al. Abnormal left ventricular relaxation in hypertensive patients. Clin Sci 1980;59:411s–4s.
30. Lavine SJ, Follansbee WP, Shreiner DP, et al. Pattern of left ventricular diastolic filling in chronic aortic regurgitation: a gated blood pool assessment. Am J Cardiol 1985;55:127–32.
31. Sanderson JE, Traill TA, Sutton MG, Brown DJ, Gibson DG, Goodwin JF. Left ventricular relaxation and filling in hypertrophic cardiomyopathy. Br Heart J 1978;40:596–601.
32. Von Hoff DD, Layard MW, Basa P, et al. Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med 1979;91:710–7.
33. Bristow MR, Mason JW, Billingham ME, Daniels JR. Dose-effect and structure-function relationships in doxorubicin cardiomyopathy. Am Heart J 1981;102:709–18.
34. Azuma J, Sperelakis N, Hasegawa H, et al. Adriamycin cardiotoxicity: possible pathogenic mechanisms. J Mol Cell Cardiol 1981;13:381–97.
35. Singal DK. Adriamycin does have a potentially depressant effect on left ventricular contractility. Int J Cardiol 1985;7:447–9.
36. Polak JF, Kemper AJ, Bianco JA, Parisi AF, Tow DE. Resting early peak diastolic filling rate: a sensitive index of myocardial dysfunction in patients with coronary artery disease. J Nucl Med 1982;23:471–8.
37. Janicki JS, Weber KT. Factors influencing the diastolic pressure-volume relation of the cardiac ventricles. Fed Proc 1980;39:133–40.
38. Praga C, Beretta G, Vigo PL, et al. Adriamycin cardiotoxicity: a survey of 1273 patients. Cancer Treat Rep 1979;63:827–34.